Author's response to reviews

Title: A Randomized Controlled Trial of Standard versus Intensified Tuberculosis Diagnostics on Treatment Decisions by Physicians in Northern Tanzania

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Author's response to reviews: see over
Reviewer's report

Title: A Randomized Controlled Trial of Standard versus Intensified Tuberculosis Diagnostics on Treatment Decisions by Physicians in Northern Tanzania

Version: 2 Date: 29 May 2013

Reviewer: Violet N Chihota

Reviewer's report:

The authors set to investigate if use of culture had an impact on patient outcomes/management of TB in Tanzania a resource limited setting. They conducted a randomised trial in Northern Tanzania. They found that

Major comments:

The authors mention that they enrolled adults defined as equal or more than 6 years of age. Is this correct? I would imagine that getting consent for some of these (less than 18) and the those defined herein as children (less than 6 years) would not be possible but rather get accent from parents/guardians? How was consenting done for children? This raised major ethical concerns.

The manuscript has been clarified to document the fact that children <6 years of age were analyzed as adults, however for purposes of consent all participants <18 years of age required parental or guardian consent.

Minor Comments

In abstract under results the authors mention that at eight weeks 100% of participants in follow up period were receiving appropriate care. This sentence needs to be rephrased to make clear the denominators. Also they should avoid just putting a percentage without clearly showing the numbers and denominators.

The denominator is already in the sentence (n=22), however I have moved it to a different location to make it more clear.

Introduction

Need to include data on TB prevalence/incidence in Tanzania to ensure the
extent of the problem is well defined.

While I did state that Tanzania was among the highest 22 TB burden countries in the world, I have added some information about the incidence that was measured at the time this study was going on.

Methods

Need to make clear in methods what study design was used and perhaps make clear that this was individually randomised and not cluster randomised.

I have clarified this in the methods.

The authors mention that one sputum was taken at enrolment and subsequent specimens the following two mornings. How many subsequent specimens were taken?

I have clarified this in the methods.

Why was TST done?

Originally the study was designed to be much bigger, and the TST was added in attempts to gather some information about prevalence of TST positivity in Tanzanian TB suspects by HIV status and CD4 count status. However in the end it was utilized as part of the information that went to clinicians in order that they make a final determination of whether the patient had TB or not.

Participants were referred for treatment to two different centres. Was the management the same at these two referral centres? This needs to be made clear otherwise it will be difficult to generalise the findings on outcomes.

It has been clarified that the management of patients with TB was the same from both locations. However, the management of patients not confirmed to have TB was different depending on various circumstances, even within the institutions, and was at the discretion of treating clinicians. I agree with the reviewer that in a larger study systematic differences at the two enrollment sites might have altered the outcomes of the study, but because the study was small, these differences would be very difficult to detect. In addition, it is important that the procedures followed reflect the unadulterated realities of follow up in the current system available to patients, as this is one of the points of the study: utilizing TB culture in a set-up as fragile as ours as it relates to follow up presents major logistical challenges that need to be considered prior to roll-out.

Under laboratory procedures, unless authors make clear that further to assessing unconcentrated sputum in the intensified diagnostic group, concentrated sputum was assessed and that culture was performed, the distinction between the two
I am not certain where the lack of clarity is in the manuscript in this section, since it states that all participants underwent unconcentrated AFB but that those randomized to intensified diagnostics underwent concentrated smears and culture. However, the further delineate, I have added the word “only” to emphasize that only those participants randomized to the intensive arm had concentrated sputum and culture.

Results

In the methods section, the authors mention that the study was implemented in both hospitalised and out-patients. However it is not clear from the results what proportion were hospitalised vs outpatients. It may be very difficult to generalise the results from hospitalised patients as they are more likely to be sicker. Is suppose this is why there was high early mortality.

Only 4/70 patients were recruited from outpatient so indeed this was one of the reasons for higher mortality. Nonetheless the fact that the patients enrolled had not sought treatment earlier or had not been properly diagnosed earlier makes an important statement. These data have been added to Table 1 in order that readers may be fully aware of the data.

If more than one specimen was collected, surely the results will be different across the specimens in some cases. How were discrepant results handled.

What TB case definitions were used? This is not very clear.

On page 7 it states that patients who had at least one sputum smear positive or at least one GA or sputum culture positive were considered to have confirmed TB. We also stated in the results that 92.9% of the participants provided at least 2 specimens.

The authors mention that 358/3249 patients met the criteria for TB? Do they mean were TB suspects? In the inclusion criteria it is clear that they were targeting TB suspects for enrolment. There was a lot of screening failures for the study and wonder why this many participants were screened ie 3249. Seems some definitions should be included in the methods to make clear who met the criteria to be included in study.
I have clarified the results section to state that 358 (11.2%) met clinical criteria for suspect TB. The inclusion criteria for the study are very clearly stated in the methods under the section Inclusion Criteria. It is true that there were a large number of patients screened in order to find those who met the inclusion criteria. However, this was how the study was designed and these were the realities of the patients hospitalized at the included institutions.